REMARKS

Claim amendments

Claims 5, 8, 11, and 13-21 are rejected and are under examination. Claim 13 has been amended to recite that the treatment occurs without significant ototoxicity. Support for this amendment can be found in the specification at, for example, paragraphs [0037] and [0074]. Claims 18 and 19 have been amended to recite a specific range of compound. Support for this amendment can be found in the specification at, for example, pages 17 – 19, Paragraphs [0055] and [0056]. Claim 20 has been amended to clarify the claim dependency. Claim 21 has also been amended to clarify the claim dependency.

Objections

Claim 19 is objected to as allegedly being of improper dependent form for failing to limit the subject matter of the previous claim.

Applicants have amended claims 18 and 19 so that claim 19 is now further limiting of claim 18. Withdrawal of this object is respectfully requested.

Rejections under 35 U.S.C. §112

Claims 20 and 21 stand rejected under 35 U.S.C. 112, second paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 20, there is allegedly insufficient antecedent basis for the limitation of "hearing loss" in claim 13.

Applicants have amended claim 13 to recite that the treatment occurs without significant ototoxicity. Applicants have amended claim 20 to recite that the lack of significant ototoxicity is indicated by stable hearing of said individual. Withdrawal of this rejection is respectfully requested.

With regard to claim 21, there is allegedly insufficient antecedent basis for the limitation of " wherein an otic inflammatory response" in claim 13.

Applicants have amended claim 21 to recite that the treatment is indicated by a reduction in an otic inflammatory response in said treated individual relative to an untreated individual. Applicants believe that this amendment renders the rejection moot and withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §102 and § 103

Claims 5, 8, 11 and 13-21 are rejected under 35 U.S.C. § 103 as being unpatentable over Avidano et al. in view of Grote et al. (USPN 6,670,327) and further in view of Brake et al. (USPN 4,752,576).

It allegedly would have been obvious to one of ordinary skill to treat patients with otitis media with a perforated tympanic membrane with a combination of alpha 1-antitrypsin and ilomastat iirrespective of the cause of how the perforations are caused since the combination statistically decrease protease activity which is beneficial in the treatment of otitis media. The motivation to employ this combination allegedly comes from Avidano et al., teaching that this combination is more effective in treatment regiment than either ilomastat or alpha1-antitrypsin alone.

To emply corticosteroid to Avidano's regimen would allegedly have been obvious because all of the components are well known and corticosteroids are known by Grote et al. for the treatment of otitis media.

It allegedly would have been obvious to employ recombinant AAT because Brake teach the method of producing AAT by recombinant methods in yeast.

Applicants traverse the rejection for the following reasons. Applicants have amended claim 13 to recite that the otitis media is treated without significant ototoxicity.

Avidano discloses *in vitro* assays for proteases on samples obtained from patients with otorrhea resulting from tympanic membrane perforations or pressure-equalization tubes. Avidano demonstrates *in vitro* protease inhibition with AAT and ilomastat.

However, Avidano fails to disclose any methods of treatment. The Examiner agrees that Avidano does not teach the actual *in vivo* treatment of an individual having otitis media with a a perforated typanic membrane.

Grote discloses the use of corticosteroids for the treatment of otitis media.

Brake teaches a method of producing AAT by recombinant methods in yeast.

The claimed invention recites a method of treating an individual having otitis media and a perforated tympanic membrane comprising administering an effective, nonototoxic amound of rAAT to the middle ear by topical application to the external auditory canalwherein the otitis media is treated without significant ototoxicity.

The Applicants respectfully submit that the Examiner has failed to make out a *prima facie* case of obviousness. In order to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999).

Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531.

Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, the references fail to teach or suggest all of the claim elements. Specifically, none of the references, either alone or when combined, teach or suggest a method that

includes delivering to any individual, much less an individual having otitis media and a perforated tympanic membrane, an effective, nonototoxic amount of recombinant AAT to the middle ear by topical application to the external auditory canal wherein the otitis media is treated without significant ototoxicity. As noted previously, Avidano fails to teach any method of treatment. Grote does disclose treatment methods with corticosteroids but does not teach the use of protease inhibitors including rAAT and /or ilomastat. Also, Brake fails to disclose any treatment methods. Accordingly, there is no teaching of the use of recombinant AAT for administration to the middle ear in the absence of significant ototoxicity.

More importantly, even if all of the claim elements were present, the teachings of the references would not have provided a reasonable expectation of success in practicing the invention as claimed.

The Examiner stated that it would have been obvious in view of Avidano et al. that "[t]he results of decrease in otic inflammatory response is reduces in the treated individual relative to an untreated individual"..."because Avidano et al's vitro data shows statistically significant ($p<0.05$) decrease in protease activity was observed in otorrhea sample collected from the patient suffering from otitis media. One of ordinary skill in the art would allow in *vitro* data shown by Avidano et al. as a surrogate for *in vivo* behavior." (page 6)

Applicants traverse the rejection. Specifically, Applicants submit that the skilled artisan would not have had a reasonable expectation of success in practicing the invention *as claimed* based on the teachings of the references.

First, the skilled artisan would be a person with knowledge of the treatment of otitis media in patients with a perforated tympanic membrane. Such individuals would know that there are many drugs, such as antibiotics, which may be effective in treating bacterial infections, but which absolutely cannot be used in patients with perforated tympanic membranes because such compounds are ototoxic, resulting in hearing loss. As has been noted previously, in that subset of otitis media cases presenting with perforated

tympanic membrane, any compound applied topically to the external canal can readily gain access to the middle ear, and thus to the site of infection and inflammation. In these cases, however, the potential toxicity of therapeutic agents is a critical clinical concern. *See, e.g.*, Roland *et al.*, "Animal ototoxicity of topical antibiotics and the relevance to clinical treatment of human subjects," *Otolaryngol. Head Neck Surg.* 130:S57-S78 (2004) and Matz *et al.*, "Ototoxicity of ototopical antibiotic drops in humans," *Otolaryngol. Head Neck Surg.* 130:S79-S82 (2004).

Indeed, even Avidano refers to the speculative nature of treating individuals. As noted in the last paragraph of p. 350 of Avidano it is noted that "[f]urther study will be required to gain a better understanding of the various types of proteases present *and to determine the clinical utility of specific protease inhibitors* in all types of chronic otitis." Thus, the primary reference itself, calls into question the likelihood of success in using rAAT alone or in combination with other agents to treat individuals with an effective and nonototoxic amount of the agents.

To this end, Applicants remind the Examiner that the claimed invention must be considered as a whole (see MPEP 2141.02 and *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. cir. 1983)). That is, the examiner appears to have impermissibly distilled the invention to a method of treating a patient with the protease inhibitors disclosed in Avidano. However, what the Examiner has not addressed is the uncertainty and potential ototoxicity associated with actual treatment. The claims, in contrast, require the administration of an effective and nonototoxic amount of rAAT wherein there is no significant ototoxicity, elements neither taught or suggested in the cited references.

As noted previously, prior to applicants' discovery, it could not be predicted whether AAT -- or inhibitors of matrix metalloproteases, notably ilomastat, or ilomastat in combination with AAT -- would prove sufficiently nonototoxic as to permit effective topical administration in the setting of a perforated tympanic membrane. Indeed, with agents drawn from a wide range of chemical classes having already, in some cases

tragically, proven ototoxic,[1] the art instead clearly counsels caution in attempting topical therapy with novel agents. Given such caution, the cited art could not have provided a reasonable expectation that an effective, yet nonototoxic, dose of AAT or ilomastat could found that would permit successful treatment of otitis media in the setting of perforated tympanic membrane in the absence of significant ototoxicity.

Applicants submit, therefore, that the Examiner has not established a *prima facie* case of obviousness *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art."). With failure of the *prima facie* case, the burden of production has not properly been shifted to applicants, and applicants are entitled, without more, to their claims. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

Furthermore, Applicants respectfully submit that the ototoxicity art clearly teaches away from the use of novel compounds as topical agents, a secondary indicium of the nonobviousness of applicants' topical administration of antiprotease in the clinical context of perforate tympanic membranes.

Applicants respectfully submit that the claims as now pending would have been nonobvious over the art of record, and that the rejection is in error and should be withdrawn.

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[1] See Roland *et al.*, Table 1.

CONCLUSION

Applicants submit that the present application is in condition for allowance, and respectfully request the same. If the Examiner believes that any matters remain outstanding prior to passing this case to issue, however, applicants respectfully request that the Examiner call the undersigned attorney, newly of record, for a telephonic interview.

Respectfully submitted,

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